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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/902,713
Filing Date: July 10, 2001
Appellant(s): GODDARD ET AL.

Leslie Mooi
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 13 September 2005 appealing from the Office action mailed 13 January 2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

09/904,766, also on appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is incorrect.

The amendment after final rejection filed on 14 March 2005 has been entered.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is essentially correct. However, Appellant's statement that "As shown in Example 92 and Table 9 of the specification, PRO269 showed approximately 2-3.5 fold amplification in 8 primary lung tumors and tumor cell lines. (see page Table 9)" may be misleading. Example 92 and Table 9 shows that PRO269 **genomic DNA** is amplified in several lung tumor samples; however, the specification does not show that PRO269 **protein** is amplified or overexpressed in any cancer tissues.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Pennica et al., 1998, PNAS USA 95:14717-14722.

Konopka et al., Proc. Natl. Acad. Sci. (1986) 83:4049-4052.

Chen et al., 2002, Molecular and Cellular Proteomics 1:304-313.

Hu et al., 2003, Journal of Proteome Research 2:405-412.

LaBaer, 2003, Nature Biotechnology 21:976-977.

Haynes et al., 1998, Electrophoresis 19:1862-1871.

Hanna et al., 1999, Pathology Associates Medical Laboratories.

Gygi et al., 1999, Mol. Cell. Biol. 19:1720-1730.

Lian et al., 2001, Blood 98:513-524.

Fessler et al., 2002, J. Biol. Chem. 277:31291-31302.

Greenbaum et al., 2003, Genome Biology 4:117.1-117.8.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 39-443 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility.

The claims are directed to antibodies that specifically bind isolated polypeptides comprising the amino acid sequence of SEQ ID NO: 96. Claims are also presented to such antibodies which are monoclonal, humanized, fragments, or labeled. The specification teaches how to make such antibodies that bind the polypeptide of SEQ ID NO: 96. The question of whether or not such antibodies have utility depends upon whether or not the polypeptide to which they bind has utility. The specification teaches that the polypeptide of SEQ ID NO: 96, also known as PRO269, is a membrane-bound polypeptide with a single transmembrane domain. PRO269 does not have significant structural similarity to any fully characterized polypeptides. There is no biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner, or any other specific feature that is disclosed as being associated with PRO269 polypeptide. Without any information as to the specific properties of PRO269, the mere identification of such as being a membrane-bound polypeptide possessing a single transmembrane domain is not sufficient to impart a well-established utility to the polypeptides or the antibodies which specifically bind them. The specification contains numerous asserted utilities for PRO269, including use as molecular weight markers, therapeutic agents, and for the production of antibodies. None of these asserted utilities is specific for the disclosed PRO269 polypeptide, as each of the aforementioned utilities could be asserted for any naturally occurring polypeptide, and further, as none of the asserted utilities requires any feature or activity that is specific to the disclosed PRO269.

At pages 222-235, a gene amplification assay discloses that genomic DNA

encoding PRO269 had a ΔCt value of at least 1.0 for eight out of seventeen lung tumor samples. Genomic DNA encoding PRO269 was not amplified in any of the seventeen colon tumor samples. The specification asserts that amplification is associated with overexpression of the gene product, indicating that the polypeptides (and the antibodies that bind them) are useful targets for therapeutic intervention in certain cancers such as colon, lung, breast and other cancers and diagnostic determination of the presence of those cancers. However, the art shows that amplification data for genomic DNA have no bearing on the utility of the encoded polypeptides. In order for PRO269 polypeptides to be overexpressed in lung tumors, amplified genomic DNA would have to correlate with amplified mRNA, which in turn would have to correlate with amplified polypeptide levels. The art discloses that such correlations cannot be presumed. Regarding the correlation between genomic DNA amplification and increased mRNA expression, see Pennica et al. (1998, PNAS USA 95:14717-14722), who disclose that:

> "An analysis of *WISP*-1 gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of *WISP*-3 RNA was seen in the absence of DNA amplification. In contrast, *WISP*-2 DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient."

See p. 14722, second paragraph of left column; pp. 14720-14721, "Amplification and Aberrant Expression of *WISPs* in Human Colon Tumors." See also Konopka et al. (Proc. Natl. Acad. Sci. (1986) 83:4049-4052), who state that "Protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Ph1 template" (see abstract). Even if increased mRNA levels

could be established for PRO269, it does not follow that polypeptide levels would also be amplified. Chen et al. (2002, Molecular and Cellular Proteomics 1:304-313) compared mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas. Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al. clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (p. 304) and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pp. 311-312). Also, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). One of the authors of this paper, Dr. LaBaer, made an even stronger statement that reports of mRNA or protein changes of as little as two-fold are not uncommon, and although changes of this magnitude may turn out to be important, **most** are attributable to disease-independent differences between the samples (emphasis added; 2003, Nature Biotechnology 21:976-977).

The art also shows that mRNA (transcript) levels do not correlate with

polypeptide levels in normal tissues. See Haynes et al. (1998, Electrophoresis 19:1862-1871), who studied more than 80 polypeptides relatively homogeneous in half-life and expression level, and found no strong correlation between polypeptide and transcript level. For some genes, equivalent mRNA levels translated into polypeptide abundances which varied more than 50-fold. Haynes et al. concluded that the polypeptide levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Gygi et al. (1999, Mol. Cell. Biol. 19:1720-1730) conducted a similar study with over 150 polypeptides. They concluded that

> "the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data. Indeed, for some genes, while the mRNA levels were of the same value the protein levels varied by more than 20-fold. Conversely, invariant steady-state levels of certain proteins were observed with respective mRNA transcript levels that varied by as much as 30-fold. Our results clearly delineate the technical boundaries of current approaches for quantitative analysis of protein expression and reveal that simple deduction from mRNA transcript analysis is insufficient"

(See Abstract). Lian et al. (2001, Blood 98:513-524) show a similar lack of correlation in mammalian (mouse) cells (see p. 514, top of left column: "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels."). See also Fessler et al. (2002, J. Biol. Chem. 277:31291-31302) who found a "[p]oor concordance between mRNA transcript and protein expression changes" in human cells (p. 31291, abstract). Greenbaum et al. (2003, Genome Biology 4:117.1-117.8) cautions against assuming that mRNA levels are generally correlative of protein

levels. The reference teaches (page 117.3, 2nd column) that primarily because of a limited ability to measure protein abundances, researchers have tried to find correlations between mRNA and the limited protein expression data, in the hope that they could determine protein abundance levels from the more copious and technically easier mRNA experiments. To date, however, there have been only a handful of efforts to find correlations between mRNA and protein expression levels, most notably in human cancers and yeast cells. And, for the most part, they have reported only minimal and/or limited correlations. The reference further teaches (page 117.4, 2nd column) that there are presumably at least three reasons for the poor correlations generally reported in the literature between the level of mRNA and the level of protein, and these may not be mutually exclusive. First, there are many complicated and varied post-transcriptional mechanisms involved in turning mRNA into protein that are not yet sufficiently well defined to be able to compute protein concentrations from mRNA; second, proteins may differ substantially in their *in vivo* half lives; and/or third, there is a significant amount of error and noise in both protein and mRNA experiments that limit our ability to get a clear picture. The reference further notes (page 117.6, page 2nd column) that to be fully able to understand the relationship between mRNA and protein abundances, the dynamic processes involved in protein synthesis and degradation have to be better understood.

Therefore, data pertaining to PRO269 genomic DNA do not indicate anything significant regarding the claimed PRO269 polypeptides or the antibodies that bind them. The data do not support the specification's assertion that PRO269 polypeptides or their antibodies can be used as a cancer diagnostic agent or as a therapeutic drug

development target. Significant further research would have been required of the skilled artisan to reasonably confirm that PRO269 polypeptide is overexpressed in any cancer to the extent that it could be used as a cancer diagnostic agent or therapeutic drug development target, and thus the asserted utility is not substantial. In the absence of information regarding whether or not PRO269 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO269 **polypeptides or antibodies** as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Claims 39-43 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

(10) Response to Argument

At p. 4 of the Brief, Appellant argues that the patentable utility of PRO269 antibodies is based on the gene amplification data for the gene encoding the PRO269 polypeptide. Appellant states that the specification shows significant amplification of the gene encoding PRO269 in eight different lung tumor samples. Appellant refers to the declaration of Dr. Goddard (submitted under 37 C.F.R. § 1.132 on 21 February 2003) as explaining that a gene that is amplified at least 2-fold by the disclosed gene amplification assay in a tumor sample relative to a normal sample is useful for the diagnosis of cancer, for monitoring cancer development, and/or for measuring the efficacy of cancer therapy. Appellant concludes that one of ordinary skill in the art would find it credible that PRO269 polypeptides and the claimed antibodies that bind the PRO269 polypeptides have utility as markers for the diagnosis of lung tumors. This has been fully considered but is not found to be persuasive for the following reasons. The art indicates that gene amplification data do not correlate with increased mRNA levels or increased polypeptide levels (see Pennica et al., Konopka et al., Haynes et al., Gygi et al., Lian et al., Fessler et al., Hu et al., LaBaer, Chen et al., Greenbaum et al.). Since the instant claims are directed to antibodies that bind polypeptides, this is a major concern. The Goddard declaration was not found to be sufficient to overcome the rejection; however, the Goddard declaration will be addressed at length later in this answer.

From p. 4 to p. 5 of the Brief, Appellant criticizes the references used to support the rejection, and states that the preponderance of the totality of the evidence indicates that it is more likely than not that one of ordinary skill in the art would not doubt the truth

of the statement of utility. Specifically, at p. 5 of the Brief, Appellant argues that the combined teachings of Pennica et al. and Konopka et al. are not directed to genes in general but to a single gene or genes within a single family. Appellant urges that their teachings cannot support a general conclusion regarding correlation between gene amplification and mRNA or polypeptide levels. Appellant argues that Orntoft et al., Hyman et al. and Pollack et al. teach that, in general, gene amplification increased mRNA expression. Appellant points to the Polakis declaration (submitted under 37 C.F.R. § 1.132 on 07 July 2004) as establishing that there is a general correlation between mRNA levels and polypeptide levels. Appellant asserts that the research community believes that the information obtained from gene chips is useful. Finally, Appellant concludes that, while there may be exceptions, there is generally a good correlation between gene amplification, mRNA levels and polypeptide levels, and thus the gene amplification data for PRO269 conveys utility to the claimed PRO269 polypeptides. This has been fully considered but is not found to be persuasive. While Pennica et al. and Konopka et al. are directed to small numbers of genes, the instant application concerns only one gene as well. Furthermore, Haynes et al., Gygi et al., Lian et al., Fessler et al., Hu et al., Chen et al., LaBaer, and Greenbaum et al. all speak to larger sets of genes and constitute evidence that polypeptide levels cannot be predicted from mRNA levels in general. The Polakis declaration will be addressed in detail later in this answer. Regarding gene chips, it is submitted that evidence of financial success is not relevant to utility or enablement. Also, the chips may provide useful information about genes, but not polypeptides or the antibodies that bind them.

Finally, products that provide only potential or preliminary results may also sell well in the research community since the researcher who buys them may plan to follow up any preliminary results obtained from the chips with experiments directed at measuring polypeptide levels.

At p. 6 of the Brief, Appellant argues that, even if there were no correlation between gene amplification and increased mRNA/polypeptide expression, an antibody that binds a polypeptide encoded by a gene that is amplified in cancer would still have utility in that simultaneous testing of gene amplification and gene product overexpression enables more accurate tumor classification, leading to a better determination of a suitable therapy, as demonstrated by the real-world example of the breast cancer marker HER-2/neu. Appellant points to the Ashkenazi declaration (submitted under 37 C.F.R. § 1.132 on 24 October 2003) as supporting this point. This has been fully considered but is not found to be persuasive, since the specification does not disclose that the PRO269 polypeptide levels increase **or** stay the same. Further research would be needed to reasonably confirm whether or not there is a change in PRO269 polypeptide levels in cancers showing gene amplification of PRO269 gene. Therefore, the asserted utility is not substantial, as the real-world use has not been established. The proposed use of the PRO269 antibodies as claimed in this application are simply starting points for further research and investigation into potential practical uses of the polypeptides. The Ashkenazi declaration (submitted under 37 C.F.R. § 1.132 on 24 October 2003) will be addressed in detail later in this answer.

At the bottom of p. 6 of the Brief, Appellant argues that, since PRO269 antibodies have utility in the diagnosis of cancer, they are also enabled. Appellant urges that the skilled artisan would know how to use the claimed antibodies in cancer diagnosis based on the disclosure. This has been fully considered but is not found to be persuasive since the PRO269 antibodies have no utility for the reasons set forth in the rejection under 35 U.S.C. § 101, above, they also are not enabled.

At pp. 7-10 of the Brief, Appellant reviews the legal standard for utility, with which the examiner takes no issue.

At p. 10 of the Brief, Appellant argues that the data in Example 92 (starting at p. 222 of the specification) describes results of a gene amplification assay. Appellant characterizes the assay as being capable of quantitatively measuring the level of gene amplification in a sample. Appellant asserts that gene amplification is an essential mechanism for oncogene activation. Appellant reviews how the assay was performed, and reports that the gene encoding PRO269 was significantly amplified (2.056-fold to 3.482-fold) in eight lung tumors. At p. 11 of the Brief, Appellant argues that it is well known that gene amplification occurs in most solid tumors, and is generally associated with poor prognosis. Appellant refers to the declaration of Dr. Goddard, submitted under 37 C.F.R. § 1.132 on 21 February 2003. Appellant quotes from p. 3 of the declaration as giving an expert opinion that a 2-fold increase in gene copy number in a tumor sample relative to a non-tumor sample is significant and useful. Appellant concludes that one skilled in the art would consider the amplification of the gene encoding PRO269 in eight lung tumors is credible based upon the facts in the Goddard

declaration. This has been fully considered but is not found to be persuasive. This line of argument and the Goddard declaration are relevant to the utility of the PRO269 **DNA**, but not the PRO269 **polypeptide or antibodies**. As discussed above, the art shows that increased DNA levels are not predictive of increased mRNA levels, and that increased mRNA levels are not predictive of increased polypeptide levels.

In the paragraph bridging pp. 11-12 of the Brief, Appellant quotes the specification regarding amplification being associated with overexpression of the gene product, indicating that polypeptides and their antibodies are useful targets for therapeutic intervention in certain cancers, and as diagnostic agents. This has been fully considered but is not found to be persuasive, since this assertion is completely unsupported by any evidence, and the art provides evidence to the contrary. Specifically, Pennica et al. (1998, PNAS USA 95:14717-14722), show a lack of correlation between gene amplification and overexpression in two out of three WISP genes. Konopka et al. (Proc. Natl. Acad. Sci. (1986) 83:4049-4052) state that polypeptide expression correlated with mRNA levels, but not gene amplification for the abl gene. Even if increased mRNA levels could be established for PRO269, it does not follow that polypeptide levels would also be amplified. Chen et al. (2002, Molecular and Cellular Proteomics 1:304-313) compared mRNA and polypeptide expression for a cohort of genes in the same lung adenocarcinomas. Only 17% of 165 polypeptide spots or 21% of the genes had a significant correlation between polypeptide and mRNA expression levels. Chen et al. clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein

products" (p. 304) and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pp. 311-312). Also, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). One of the authors of this paper, Dr. LaBaer, made an even stronger statement that reports of mRNA or protein changes of as little as two-fold are not uncommon, and although changes of this magnitude may turn out to be important, **most** are attributable to disease-independent differences between the samples (emphasis added; 2003, Nature Biotechnology 21:976-977). Finally, the art also shows that transcript levels do not correlate with polypeptide levels in normal tissues. See Haynes et al. (1998, Electrophoresis 19:1862-1871), who studied more than 80 polypeptides relatively homogeneous in half-life and expression level, and found no strong correlation between polypeptide and transcript levels. For some genes, equivalent mRNA levels translated into polypeptide abundances which varied more than 50-fold. Haynes et al. concluded that the polypeptide levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Gygi et al.

(1999, Mol. Cell. Biol. 19:1720-1730) conducted a similar study with over 150 polypeptides. They concluded that

> "the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data. Indeed, for some genes, while the mRNA levels were of the same value the protein levels varied by more than 20-fold. Conversely, invariant steady-state levels of certain proteins were observed with respective mRNA transcript levels that varied by as much as 30-fold. Our results clearly delineate the technical boundaries of current approaches for quantitative analysis of protein expression and reveal that simple deduction from mRNA transcript analysis is insufficient"

(See Abstract). Lian et al. (2001, Blood 98:513-524) show a similar lack of correlation in mammalian (mouse) cells (see p. 514, top of left column: "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels."). See also Fessler et al. (2002, J. Biol. Chem. 277:31291-31302) who found a "[p]oor concordance between mRNA transcript and protein expression changes" in human cells (p. 31291, abstract). Finally, Greenbaum et al. (2003, Genome Biology 4:117.1-117.8) cautions against assuming that mRNA levels are generally correlative of protein levels. The reference teaches (page 117.3, 2nd column) that primarily because of a limited ability to measure protein abundances, researchers have tried to find correlations between mRNA and the limited protein expression data, in the hope that they could determine protein abundance levels from the more copious and technically easier mRNA experiments. To date, however, there have been only a handful of efforts to find correlations between mRNA and protein expression levels, most notably in

human cancers and yeast cells. And, for the most part, they have reported only minimal and/or limited correlations. The reference further teaches (page 117.4, 2nd column) that there are presumably at least three reasons for the poor correlations generally reported in the literature between the level of mRNA and the level of protein, and these may not be mutually exclusive. First, there are many complicated and varied post-transcriptional mechanisms involved in turning mRNA into protein that are not yet sufficiently well defined to be able to compute protein concentrations from mRNA; second, proteins may differ substantially in their *in vivo* half lives; and/or third, there is a significant amount of error and noise in both protein and mRNA experiments that limit our ability to get a clear picture. The reference further notes (page 117.6, page 2nd column) that to be fully able to understand the relationship between mRNA and protein abundances, the dynamic processes involved in protein synthesis and degradation have to be better understood.

At the top of p. 12 of the Brief, Appellant argues that their position is based on the overwhelming evidence that the gene encoding PRO269 is significantly amplified. Appellant urges that, based on the working hypothesis among those skilled in the art that if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level, one skilled in the art would simply accept that since the PRO269 gene is amplified, the PRO269 polypeptide would be more likely than not over-expressed. Appellant concludes that no further experiments would be necessary to determine how to use the claimed polypeptide, the specification contains clear guidance on how to interpret and use the data relating to the PRO269 polypeptide expression, and that PRO269 polypeptides have utility in the diagnosis of cancer. This has been fully

considered but is not found to be persuasive. First, the preponderance of the totality of the evidence indicates that those skilled in the art do not presume that an amplified gene correlates with an amplified polypeptide. See Haynes et al., Gygi et al., Lian et al., Fessler et al., Hu et al., Chen et al., LaBaer, and Greenbaum et al. Second, further experiments would be required to reasonably confirm that PRO269 polypeptide levels are different in cancerous versus healthy tissues. Finally, the specification contains no data pertaining to the PRO269 *polypeptide*.

At p. 13 of the Brief, Appellant argues that the Konopka and Pennica references do not support the utility rejection. Specifically, Appellant characterizes Konopka et al. as being limited to the abl gene, and not speaking to genes in general. Appellant concludes that the examiner must show evidence that it is more likely than not that the correlation does not exist, and that a *prima facie* case of lack of utility has not been made. Appellant characterizes Pennica et al. as being limited to WISP genes, and does not speak to the correlation of gene amplification and protein expression for genes in general. Appellant argues that the working hypothesis among those skilled in the art is that there is a correlation between gene amplification and protein overexpression. Appellant points out that there was such a correlation for WISP-1 as disclosed by Pennica et al. This has been fully considered but is not found to be persuasive. Pennica et al. and Konopka et al. are relevant even though they are not reviews of gene amplification for genes in general because they show a lack of correlation between gene amplification and gene product overexpression. The instant case also concerns a single gene. Moreover, the rejection is based on more evidence than just Pennica et al.

and Konopka et al. The evidence of record indicates that (1) gene amplification does not reliably correlate with increased mRNA levels (Pennica et al., Konopka et al.), and (2) increased mRNA levels do not reliably correlate with increased polypeptide levels in the majority of cases (Haynes et al., Gygi et al., Lian et al., Fessler et al., Hu et al., LaBaer, Chen et al., Hanna et al., Greenbaum et al.).

At p. 14 of the Brief, Appellant argues that Haynes et al. support Appellant's position when they state that there was a general trend between protein expression and transcript levels. Appellant also criticizes Haynes et al. for being directed to yeast genes. This has been fully considered but is not found to be persuasive because Haynes et al. clearly state "[p]rotein expression levels are not predictable from the mRNA expression levels" (p. 1863, top of left column) and "only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts" (p. 1870, under concluding remarks). Clearly, Haynes et al. are saying that mRNA levels do not predict protein levels, in general. Furthermore, research on mammalian systems revealed a similar lack of correlation between mRNA levels and polypeptide levels. See Lian et al., Fessler et al., Hu et al., LaBaer, Chen et al., Hanna et al., Greenbaum et al.

At the bottom of p. 14 of the Brief, Appellant concludes that the Patent Office has failed to meet its initial burden of proof that Appellant's claims of utility are not substantial or credible. Appellant urges that the examiner's arguments and evidence do not provide sufficient reasons to doubt the statements made by Appellant that the PRO269 polypeptide has utility. Appellant argues that the law does not require the

existence of a strong or linear correlation between mRNA levels and polypeptide levels, or a standard that DNA amplification is always associated with overexpression of the gene product. Appellant concludes that the examiner's reasoning is based on a misrepresentation of the scientific data presented in the Pennica, Konopka and Haynes references, and that an improper, heightened legal standard has been applied. Appellant states that the art indicates that, if a gene is amplified in cancer, it is more likely than not that the encoded polypeptide will be expressed at an elevated level. This has been fully considered but is not found to be persuasive. Appellant has not supported the contention that the art indicates that, if a gene is amplified in cancer, it is more likely than not that the encoded polypeptide will be expressed at an elevated level. In fact, the art shows quite the opposite.

Pennica et al. (1998, PNAS USA 95:14717-14722), show a lack of correlation between gene amplification and overexpression in two out of three WISP genes. Konopka et al. (Proc. Natl. Acad. Sci. (1986) 83:4049-4052) state that polypeptide expression correlated with mRNA levels, but not gene amplification for the abl gene. Chen et al. (2002, Molecular and Cellular Proteomics 1:304-313) state that "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pp. 311-312). Hu et al. (2003, Journal of Proteome Research 2:405-412) discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. LaBaer (2003, Nature Biotechnology 21:976-977) stated that reports of mRNA or protein changes of as little

as two-fold are not uncommon, and although changes of this magnitude may turn out to be important, **most** are attributable to disease-independent differences between the samples. Haynes et al. (1998, Electrophoresis 19:1862-1871) and Gygi et al. (1999, Mol. Cell. Biol. 19:1720-1730) found no strong correlation between polypeptide and transcript levels in numerous yeast genes. Lian et al. (2001, Blood 98:513-524) show a similar lack of correlation in mammalian (mouse) cells. Fessler et al. (2002, J. Biol. Chem. 277:31291-31302) found a poor concordance between mRNA transcript and protein expression changes in human cells. Finally, Greenbaum et al. (2003, Genome Biology 4:117.1-117.8) cautions against assuming that mRNA levels are generally correlative of protein levels. The preponderance of the totality of the evidence indicates that it is more likely than not that DNA amplification does *not* correlate with elevated polypeptide levels, and thus the rejection should be maintained.

At pp. 15-16 of the Brief, Appellant argues that ample evidence has been submitted to support the assertion that gene amplification more likely than not correlates with increased mRNA and polypeptide levels. Appellant characterizes Orntoft et al. as studying transcript levels of 5600 genes in malignant bladder cancers, many of which were linked to the gain or loss of chromosomal material and found that in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Appellant characterizes Hyman et al. as comparing DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, and found that there was evidence of a prominent global influence of copy number changes on gene expression levels. Appellant characterizes

Pollack et al. as profiling DNA copy number alteration across 6691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines, and found that one average, a 2-fold change in DNA copy number was associated with a corresponding 1.5-fold increase in mRNA levels. Appellant concludes that gene amplification is more likely than not predictive of increased mRNA and polypeptide levels. This has been fully considered but is not found to be persuasive. Orntoft et al. (Molecular and Cellular Proteomics 1:37-45, 2002) could only compare the levels of about 40 well-resolved and focused *abundant* proteins." (See abstract.) It would appear that Appellants have provided no fact or evidence concerning a correlation between the specification's disclosure of *low* levels of amplification of DNA (which were not characterized on the basis of those in the Orntoft publication) and an associated rise in level of the encoded protein. Hyman (Cancer Research 62:6240-6245) found 44% of *highly* amplified genes showed overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes were amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO269 would be correlated with elevated levels of mRNA, much less protein. Hyman does not examine protein expression. Pollack et al. is similarly limited to highly amplified genes which were not evaluated by the method of the instant

specification. None of the three references are directed to gene amplification, mRNA levels, or polypeptide levels in lung cancer.

At p. 16 to p. 17 of the Brief, Appellant addresses the comments made in the final rejection regarding the Orntoft et al., Hyman et al., and Pollack et al. references. Appellant argues that Orntoft et al. studied 1800 genes that yielded an increase or decrease in mRNA expression in two invasive tumors compared to non-invasive papillomas (also tumors), and then mapped them to chromosomal locations. Appellant argues that the chromosomal locations had already been analyzed for amplification via CGH. Appellant argues that Orntoft et al. found that in general areas with strong gain of chromosomal material contained a cluster of genes having increased mRNA expression. Appellant quotes from Orntoft et al. as stating that a highly significant correlation was observed between the level of CGH ratio change (DNA copy number) and alteration detected by arrays (mRNA levels). Appellant argues that Orntoft et al. studied mRNA relation to protein levels and found a highly significant correlation. Appellant concludes that Orntoft et al. supports Appellant's position that proteins expressed by genes that are amplified in tumors are useful as cancer markers. Appellant also argues that there is no clear relevance of the examiner's concern that PRO269 has not been disclosed as being part of a gene cluster. This has been fully considered but is not found to be persuasive. As discussed above, Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p. 40). Orntoft et al.'s findings could only be extended to other genes in such clusters. This analysis was not done for PRO269 in the instant

specification, and so it is not clear whether or not PRO269 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the findings of Orntoft et al. cannot be extended to PRO269. Also, Orntoft et al. compared genes from non-invasive transitional cell carcinomas to genes from invasive transitional cell carcinomas. There was no comparison between genes in cancerous versus non-cancerous tissue. Thus, Orntoft et al. did not find any cancer markers. Furthermore, Orntoft et al. could only compare the levels of about 40 well-resolved and focused *abundant* proteins. (See abstract.) Appellant has provided no fact or evidence concerning a correlation between the specification's disclosure of *low* levels of amplification of DNA (which were not characterized on the basis of those in the Orntoft publication) and an associated rise in level of the encoded protein. Finally, Orntoft et al. did not study lung cancer.

At p. 17 of the Brief, Appellant argues that the examiner has mischaracterized the methods used by Hyman et al. and Pollack et al. Appellant urges that these papers did not use traditional CGH, but rather did gene-by-gene analysis across all chromosomes. Appellant characterizes Hyman et al. as studying 13,824 clones for gene expression and gene copy number in 14 breast cancer cell lines. Appellant quotes from Hyman et al. regarding their finding that up to 44% of the highly amplified genes were overexpressed compared with only 6% for genes with normal copy number. Appellant further quotes from Hyman et al. regarding the cDNA/microarray technique enables the direct correlation of copy number and expression data on a gene-by-gene basis throughout the genome. Appellant concludes that Hyman et al. performed an analysis on a gene-by-gene basis, and clearly shows that it is more likely than not that a

gene which is amplified in tumor cells will have increased gene expression. This has been fully considered but is not found to be persuasive. As discussed above, Hyman et al. found 44% (less than half) of *highly* amplified genes showed overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes were amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. This is direct evidence that it is "more likely than not" that gene amplification does *not* correlate with increased mRNA expression. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO269 would be correlated with elevated levels of mRNA, much less protein. Also, Hyman et al. did not evaluate lung cancer.

From p. 17 to 18 of the Brief, Appellant characterizes Pollack et al. as studying DNA copy number across 6691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines. Appellant quotes from Pollack et al., saying that parallel microarrays measurements of mRNA levels reveal the remarkable degree to which variation in gene copy number contributes to variation in gene expression in tumor cells, and that genome-wide, of 117 high-level DNA amplifications, 62% are found associated with at least moderately elevated mRNA levels and 42% associated with highly elevated mRNA levels. Appellant concludes that the Pollack et al. reference constitutes evidence that it is more likely than not that a gene which is amplified in tumor cells will have increased gene expression. This has

been fully considered but is not found to be persuasive. A s discussed above, Pollack et al. also used CGH technology, concentrating on large chromosome regions showing high amplification (p. 12965). Pollack et al. is similarly limited to *highly* amplified genes which were not evaluated by the method of the instant specification, and did not test for protein expression levels. Also, Pollack et al. did not study lung cancer.

At pp. 18-19 of the Brief, Appellant refers to the declaration of Dr. Polakis, submitted under 37 C.F.R. § 1.132 with the response filed 03 November 2004. Appellant characterizes the declaration as setting forth Dr. Polakis' experience with microarray analysis wherein approximately 200 gene transcripts present in human tumor cells were found to be at significantly higher levels than in corresponding normal human cells. The declaration goes on to state that antibodies binding to about 30 of these tumor antigens were prepared, and mRNA and protein levels compared. The declaration states that in approximately 80% of the cases, the researchers found that increased levels of RNA correlated with changes in the level of protein. Appellant concludes that all of the submitted evidence supports Appellant's position that it is more likely than not that increased gene amplification levels predict increased mRNA and increased protein levels, thus meeting the utility standards. This has been fully considered but is not found to be persuasive. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. (1) In the instant case, the nature of

the fact sought to be established is whether or not gene amplification is predictive of increased mRNA levels and, in turn, increased protein levels. Dr. Polakis declares that 80% of approximately 200 instances of elevated mRNA levels were found to correlate with increased protein levels. (2) It is important to note that the instant specification only discloses gene amplification data for PRO269 (i.e., data regarding amplification of PRO269 genomic DNA), and does not disclose any information regarding PRO269 mRNA levels. Furthermore, there is strong opposing evidence showing that gene amplification is not predictive of increased mRNA levels in normal and cancerous tissues and, in turn, that increased mRNA levels are frequently not predictive of increased polypeptide levels. See, e.g., Pennica et al., Konopka et al., Chen et al. (who found only 17% of 165 polypeptide spots or 21% of the genes had a significant correlation between polypeptide and mRNA expression levels in lung adenocarcinoma samples), Hu et al. (who reviewed 2286 genes reported in the literature to be associates with breast cancer), LaBaer, Haynes et al., Gygi et al., Lian et al., Fessler et al., and Greenbaum et al., all discussed *supra*. (3) Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Polakis is employed by the assignee. (4) Finally, Dr. Polakis refers to facts; however, the data is not included in the declaration so that the examiner could not independently evaluate them. For example, how many of the tumors were lung tumors? How highly amplified were the genes that correlated with increased polypeptide levels?

At pp. 19-20 of the Brief, Appellant comments upon the examiner's evaluation of the Polakis declaration. Specifically, Appellant cites case law concerning the

examiner's requirement to consider all of the evidence of record anew, and that opinion evidence must be considered. Appellant also points to the utility guidelines as directing the examiner to accept an opinion from an expert. Appellant points to the statement in the Polakis declaration that it is Dr. Polakis' considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates with a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. Appellant concludes that the fact-based conclusions of Dr. Polakis would be considered reasonable and accurate by the skilled artisan. This has been fully considered but is not found to be persuasive. As discussed above, in assessing the weight to be given expert testimony, the examiner may properly consider several factors. In the instant case, the nature of the fact sought to be established is whether or not increased mRNA levels are predictive of increased polypeptide levels. The art provides strong evidence that increased mRNA levels do not correlate with increased protein levels in both healthy and cancerous tissues. See Haynes et al., Gygi et al., Lian et al., Fessler et al., Hu et al., Chen et al., and Greenbaum et al. Dr. Polakis has an interest in the case since he is employed by the assignee. Finally, while Dr. Polakis bases his findings with reference to facts, the facts are not independently provided for the examiner to draw independent conclusions. For example, it is not clear if any of the tumors were from lung, or how highly amplified the genes were that correlated with polypeptide overexpression. Based on the totality of the evidence, considering it anew, it is maintained that one skilled in the art would view the instant gene amplification data as merely preliminary with regard to whether or not mRNA or

protein levels of PRO269 are specifically amplified in lung tumors. Further research would have to be done in order to determine if PRO269 mRNA and protein are amplified and, if so, whether or not the amplification is significant enough to reasonably confirm the usefulness of PRO269 protein as a lung cancer marker. Thus, the claimed invention does not provide products or services in "currently available" to the public, and the asserted utility is not substantial.

At the bottom of p. 20 of the Brief, Appellant summarizes the conclusions drawn from the references cited so far. Appellant argues that while there are some examples in the art that do not fit within the central dogma of molecular biology that there is a correlation between polypeptide and mRNA levels, these instances are rare rather than the rule. Appellant urges that in the majority of amplified genes, the evidence (including Orntoft et al., Hyman et al., Pollack et al., the Polakis declaration) shows that gene amplification influences gene expression at the mRNA and protein levels. Appellant concludes that the examiner has not established that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Appellant argues that one skilled in the art would reasonably expect, based on the gene amplification data, that PRO269 polypeptide is also overexpressed. This has been fully considered but is not found to be persuasive. Regarding the totality of the evidence, first, the literature reports that gene amplification often does not correlate with increased mRNA levels (see Pennica et al., Konopka et al.). Second, the literature reports that increased mRNA levels do not correlate with increased polypeptide levels in healthy tissue (see Haynes et al., Gygi et al., Lian et al., Fessler et al.) or cancerous tissue (see

Hu et al., LaBaer, Chen et al., Hanna et al.). In view of this, and the fact that the specification only asserts that PRO269 polypeptides are useful as cancer diagnostic agents based on PRO269 genomic DNA amplification results (i.e., the specification does not actually show that PRO269 polypeptides are expressed at elevated levels in any cancer tissues), the totality of the evidence indicates that the skilled artisan would *not* reasonably presume that PRO269 polypeptide is overexpressed in certain lung tumors based on the disclosure regarding gene amplification without actually testing for PRO269 polypeptide overexpression. The requirement for such testing to reasonably confirm the asserted utility indicates that the asserted utility is not substantial, i.e., it is not in currently available form. In view of the totality of the evidence, the rejections for lack of utility and enablement are proper.

From p. 21 to p. 22 of the Brief, Appellant criticizes the Hu et al. reference. Specifically, Appellant criticizes Hu et al. for being based upon a statistical analysis of information from published literature rather than from experimental data. Appellant characterizes Hu et al. as being limited to estrogen-receptor-positive breast tumor only. Appellant criticizes the types of statistical tests performed by Hu et al. Appellant concludes that, based on the nature of the statistical analysis performed in Hu et al., and the fact that Hu et al. only analyzed one class of genes, the conclusions drawn by the examiner are not reliably supported. This has been fully considered but is not found to be persuasive. The asserted utility for the claimed polypeptides is based on a sequence of presumptions. First, it is presumed that gene amplification predicts increased mRNA production. Second, it is presumed that increased mRNA production

leads to increased protein production. Hu et al. is directly on point by showing that the second presumption is incorrect when designating proteins as diagnostic markers for cancer. Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). The instant specification does not disclose that PRO269 mRNA levels are expressed at 10-fold or higher levels compared with normal, matched tissue samples. Therefore, based on Hu et al., the skilled artisan would not reasonably expect that PRO269 protein can be used as a cancer diagnostic. Furthermore, Hanna et al. show that gene amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested empirically. Also, Chen et al. (2002, Molecular and Cellular Proteomics 1:304-313) compared mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas (the same type of cancer for which PRO269 tested positive). Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al. clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (p. 304) and "it is not possible to

predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pp. 311-312). The instant specification does not provide additional information regarding whether or not PRO269 mRNA or polypeptide is overexpressed in lung adenocarcinomas, and thus the skilled artisan would need to perform additional experiments to reasonably confirm such. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial. Regarding Appellant's criticism of Hu et al.'s statistical analysis, Appellant is holding Hu et al. to a higher standard than their own specification, which does not provide proper statistical analysis such as reproducibility, standard error rates, etc. Regarding Appellant's criticism of Hu et al. as being limited to a specific type of breast tumor, Hu et al. is cited as one of several pieces of evidence that gene amplification in a tumor does not correlate with mRNA overproduction or protein overproduction. When viewed with the evidence of record as a whole, there is no correlation between gene amplification, mRNA levels and protein levels. In view of the totality of the evidence, including the declarations submitted under 37 CFR 1.132 and the publications of record, the instant utility rejection is appropriate.

At p. 22 of the Brief, Appellant argues, Appellant refers to the declaration of Dr. Ashkenazi, submitted under 37 C.F.R. § 1.132. In the declaration, Dr. Ashkenazi states that, if gene amplification results in over-expression of the mRNA and corresponding gene product, then it identifies that gene product as a promising target for cancer therapy, for example by the therapeutic antibody approach. Appellant concludes that the examiner has not shown a lack of correlation between gene amplification data and

the biological significance of cancer genes. Appellant urges that a credible, specific, and substantial asserted utility has been established for antibodies that bind the PRO269 polypeptide. This has been fully considered but is not found to be persuasive. There is no evidence of record that PRO269 polypeptide is expressed at elevated levels in cancer tissue. The specification indicates that PRO269 genomic DNA is amplified in several lung tumor samples. However, this is not predictive of elevated PRO269 polypeptide levels in view of the state of the art which establishes that it is more likely than not that amplified DNA levels fail to correlate with increased mRNA (transcript) levels, and that elevated mRNA levels fail to correlate with elevated polypeptide levels. See Pennica et al., Konopka et al., Chen et al., Hu et al., LaBaer, Haynes et al., Gygi et al., Lian et al., Fessler et al., and Greenbaum et al.

From p. 23 to p. 24 of the Brief, Appellant points to the declaration of Dr.. Ashkenazi, submitted under 37 CFR 1.132 on 21 May 2004, as establishing that, even if the protein were not overexpressed, the simultaneous testing of gene amplification and gene product overexpression would enable more accurate tumor classification. Appellant concludes that such a situation would allow for better tumor classification and better determination of suitable therapy. Appellant argues that absence of overexpression is crucial information for a clinician, because it indicates that the patient should not be treated with agents that target that gene product. Appellant argues that this saves money and benefits the patients who can avoid exposure to the side effects associated with such agent. This has been fully considered but is not found to be persuasive. The specification does not disclose such further testing of gene product

overexpression. Therefore, the skilled artisan would have been required to do the testing to reasonably confirm whether or not the PRO269 polypeptide is overexpressed. In view of such requirement, the products or services based on the claimed invention are not in "currently available" form for the public. Furthermore, the specification provides no assertion that the claimed PRO269 polypeptides are useful in tumor categorization, nor does it provide guidance regarding what treatment modalities should be selected by a physician depending upon whether or not a tumor overexpresses PRO269. For example, neither the specification nor the prior art discloses an agent that targets PRO269 that is useful for cancer therapy. This is also further experimentation that would have to be performed by the skilled artisan, indicating that the asserted utility is not substantial.

At p. 24 of the Brief, Appellant argues that the gene encoding PRO269 polypeptide is amplified in at least 8 lung tumor samples. Appellant characterizes the PRO269 gene as a tumor associated gene. Appellant urges that, in the majority of amplified genes, the teachings in the art overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Appellant argues that one skilled in the art would expect the PRO269 polypeptide to be overexpressed in lung tumor tissues based on the PRO269 gene amplification data. This has been fully considered but is not found to be persuasive. In order for PRO269 polypeptides to be overexpressed in lung tumors, amplified genomic DNA would have to correlate with amplified mRNA, which in turn would have to correlate with amplified polypeptide levels. The art discloses that such correlations cannot be presumed. Regarding the correlation

between genomic DNA amplification and increased mRNA expression, see Pennica et al. (1998, PNAS USA 95:14717-14722), who disclose that there is no correlation between genomic DNA amplification and increased mRNA levels for two out of three WISP genes. Regarding correlation between amplified genomic DNA and elevated polypeptide levels, Konopka et al. (Proc. Natl. Acad. Sci. (1986) 83:4049-4052), who state that "Protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Ph1 template" (see abstract). Regarding whether or not elevated mRNA levels are generally predictive of elevated polypeptide levels in diseased tissues, Chen et al. (2002, Molecular and Cellular Proteomics 1:304-313) compared mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas. Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al. clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (p. 304) and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pp. 311-312). Also, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level,

there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). One of the authors of this paper, Dr. LaBaer, made an even stronger statement that reports of mRNA or protein changes of as little as two-fold are not uncommon, and although changes of this magnitude may turn out to be important, **most** are attributable to disease-independent differences between the samples (emphasis added; 2003, Nature Biotechnology 21:976-977). The art also shows that mRNA (transcript) levels do not correlate with polypeptide levels in normal tissues. See Haynes et al. (1998, Electrophoresis 19:1862-1871), who studied more than 80 polypeptides relatively homogeneous in half-life and expression level, and found no strong correlation between polypeptide and transcript level. For some genes, equivalent mRNA levels translated into polypeptide abundances which varied more than 50-fold. Haynes et al. concluded that the polypeptide levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Gygi et al. (1999, Mol. Cell. Biol. 19:1720-1730) reached similar conclusions on their study of over 150 polypeptides. Lian et al. (2001, Blood 98:513-524) show a similar lack of correlation in mammalian (mouse) cells (see p. 514, top of left column: "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels."). See also Fessler et al. (2002, J. Biol. Chem. 277:31291-31302) who found a "[p]oor concordance between mRNA transcript and protein expression changes" in human cells (p. 31291, abstract). Finally, Greenbaum et al. (2003, Genome Biology 4:117.1-117.8) cautions

against assuming that mRNA levels are generally correlative of protein levels. The reference teaches (page 117.3, 2nd column) that primarily because of a limited ability to measure protein abundances, researchers have tried to find correlations between mRNA and the limited protein expression data, in the hope that they could determine protein abundance levels from the more copious and technically easier mRNA experiments. To date, however, there have been only a handful of efforts to find correlations between mRNA and protein expression levels, most notably in human cancers and yeast cells. And, for the most part, they have reported only minimal and/or limited correlations. The reference further teaches (page 117.4, 2nd column) that there are presumably at least three reasons for the poor correlations generally reported in the literature between the level of mRNA and the level of protein, and these may not be mutually exclusive. First, there are many complicated and varied post-transcriptional mechanisms involved in turning mRNA into protein that are not yet sufficiently well defined to be able to compute protein concentrations from mRNA; second, proteins may differ substantially in their *in vivo* half lives; and/or third, there is a significant amount of error and noise in both protein and mRNA experiments that limit our ability to get a clear picture. The reference further notes (page 117.6, page 2nd column) that to be fully able to understand the relationship between mRNA and protein abundances, the dynamic processes involved in protein synthesis and degradation have to be better understood.

Therefore, data pertaining to PRO269 genomic DNA do not indicate anything significant regarding the claimed PRO269 polypeptides. The data do not support the specification's assertion that PRO269 polypeptides can be used as a cancer diagnostic

agent or as a therapeutic drug development target. Significant further research would have been required of the skilled artisan to reasonably confirm that PRO269 polypeptide is overexpressed in any cancer to the extent that it could be used as a cancer diagnostic agent or therapeutic drug development target, and thus the asserted utility is not substantial. In the absence of information regarding whether or not PRO269 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO269 **polypeptides** as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

At p. 24 of the Brief, Appellant argues that even if gene amplification does not result in overexpression of the encoded polypeptide, an analysis of the expression of the polypeptide is useful in determining the course of treatment, as suggested by the Ashkenazi declaration. Appellant argues that the examiner mischaracterizes the testing described in the Ashkenazi declaration as involving further characterization of the PRO269 polypeptide itself. Appellant urges that the purpose of the testing is not to further characterize the PRO269 polypeptide, but to further characterize the tumors

being sampled. Appellant concludes that the PRO269 polypeptides and antibodies which specifically bind thereto are useful in tumor categorization, the results of which become an important tool in the hands of a physician enabling selection of a treatment modality that holds the most promise for the successful treatment of a patient. This has been fully considered but is not found to be persuasive. First, testing whether or not a polypeptide is overexpressed in a particular tumor yields information regarding the tumor *and* the polypeptide itself. For example, a polypeptide can be further categorized regarding its expression pattern in healthy and diseased tissues. Second, the specification does not assert that PRO269 polypeptide is useful as a tumor categorization agent. Such is only presented in the arguments and declaration. Third, even if such were asserted in the specification as filed, the skilled artisan would still have to perform further research to reasonably confirm whether or not PRO269 polypeptide is overexpressed in any tumor, since the expression levels of PRO269 polypeptide are not disclosed in the specification. The requirement for such further research indicates that the utility is not in currently available form, i.e., it is not substantial. Finally, it is no small matter to go from information regarding protein expression levels in a tumor to designing a therapeutic regimen specific to the protein expression profile. In Hanna et al., Herceptin was discussed as a drug specific to tumors expressing HER-2/neu. Herceptin had been known prior to the publication of Hanna et al. No such drug is disclosed in the specification, nor in the prior art, regarding the PRO269 polypeptide. Identifying a drug specific for PRO269 would involve more than routine experimentation, as it would require a great amount of

experimentation (e.g., screening agents for effects on PRO269 polypeptide and on tumor), considering there is no guidance or working examples relative to such drugs in the specification or the prior art.

In conclusion, it is noted that M.P.E.P. § 2107 I states:

> A "substantial utility" defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities.

In the instant case, the asserted utility that PRO269 polypeptides are useful as diagnostic markers for cancer or as therapeutic targets for cancer drugs is not substantial in that further research is required to reasonably confirm a real world context of use. In order for PRO269 polypeptide to be useful as a cancer diagnostic or therapeutic target, there must be a detectable change in the amount or form of PRO269 polypeptide between cancerous and healthy tissue. In the instant case, the evidence of record indicates that (1) gene amplification does not reliably correlate with increased mRNA levels (Pennica et al., Konopka et al.), and (2) increased mRNA levels do not reliably correlate with increased polypeptide levels (Haynes et al., Gygi et al., Lian et al., Fessler et al., Hu et al., LaBaer, Chen et al., Hanna et al., Greenbaum et al.). In view of this, the skilled artisan would have viewed the gene amplification results as preliminary with respect to the utility of the encoded polypeptides, and would have had to experiment further to reasonably confirm whether or not PRO269 polypeptides can be used as a cancer diagnostic agent.

At pp. 24-25 of the Brief, Appellant argues that since the claimed antibodies have utility, they are also enabled. This has been fully considered but is not found to be

persuasive, since the claimed antibodies do not have utility for the reasons discussed above.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

(12) Oral Arguments

Appellant has not yet indicated whether or not oral arguments will be presented. however, if Appellant requests such, the examiner respectfully requests the opportunity to present oral arguments as well.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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